Quasi-Experimental and Interrupted Time-Series Design

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In this issue of the Journal of the Pediatric Infectious Diseases Society, Newland et al use a quasi-experimental study design. This study design, also known as a nonrandomized, postintervention design, is beneficial in infectious disease studies where complete control over the allocation and/or the timing of the intervention is not possible or is not ethical [1]. Scenarios in which randomization of the intervention is not possible include interventions implemented at a level (eg, physician, unit, hospital) other than the patient level, and those that require immediate implementation. In the first scenario, a physician who wants to study the safe transfer of patients from one unit to another would need to implement the intervention at multiple levels: the physician level, the unit level, and then at the hospital level. If the intervention in this scenario were an educational workshop on safe transfers, one would need to assume that this information would not be disseminated from the physicians who were officially “trained” and those that weren’t. This is not an appropriate assumption, as patient transfers affect multiple physicians in multiple units at multiple time points. In situations such as a meningococcal meningitis outbreak where an intervention such as antibiotic prophylaxis is needed quickly and an untreated control group (as in a randomized control trial) is unethical, a retrospective quasi-experimental design can be used to study the efficacy of the intervention.

One of the most basic quasi-experimental designs includes a pretest and posttest with no control group. This design is depicted below; O1 represents the pretest observations, X represents the intervention, and O2 represents the posttest observations after the intervention has been implemented [2]:

\[ O1 \times O2 \]

Although this design is often used, it has substantial weaknesses. Most notably, secular trends unrelated to the intervention may result in an improvement in outcome on the posttest. For instance, suppose a daycare center wants to test the efficacy of hand washing among attendees to decrease the number of influenza cases spread within the daycare center. If the pretest observations were collected during the winter months and the posttest observations were collected during the summer months, with the hand-washing intervention implemented during the spring months, then a decrease in the number of influenza cases most assuredly will be found in the posttest period. This decrease, however, is not directly associated with the intervention as other events, specifically seasonal changes in influenza prevalence, have also occurred during the same time period. Another concern with this simple design is regression to the mean. Using the same example, the investigators decide to compare the number of influenza cases in consecutive winters while implementing the hand-washing intervention during the months in between. If the intervention was implemented after a particularly busy influenza season, the investigators of this study might find a substantial decrease in the number of cases of influenza in the posttest period. The decreased number of influenza cases...
may be due to regression toward the mean, as influenza during subsequent seasons would be likely less prevalent than during the pretest period due to chance alone. There are two main strategies to overcome the weaknesses of this simple design. The collection of data at multiple time points during the pretest and posttest periods allows the investigator to examine the presence of underlying secular trends and regression to the mean over the entire time period of the study. In cases where a control group is not available, an interrupted time series is a stronger design than the simple pretest/posttest design. However, the inclusion of an untreated control group offers even more evidence that any observed changes are due directly to the intervention.

Inclusion of an untreated control group (the group under the solid line) using an interrupted time series (time = 1 to 6) creates one of the strongest quasi-experimental study designs:

\[
\text{O1 O2 O3} \times \text{O4 O5 O6}
\]

\[
\text{O1 O2 O3} \text{ O4 O5 O6}
\]

The interruption in the time series refers to the specific point at which the intervention was implemented. The inference that an intervention directly affects the outcome in the posttest period is strengthened by the presence of a control group that has never had the intervention and therefore shows no changes from the pretest to posttest period. In addition, the time series design controls for confounding effects that may be time-dependent (eg, seasonality) [1–3]. There are many considerations when designing an interrupted time series with a control group design: (1) instantaneous interventions support causation more than interventions that diffuse gradually in the population; (2) 50 or more time points (or “observations”) at a systems level are suggested to properly estimate the correlated error in the series, less than 50 time points can be used but temporality may not be as strongly established; (3) missing data at different time points would bias the difference found between pretest and posttest, as there may be an undocumented reason for the shift in observations; (4) if the outcome is a rare event, it is likely that the effect of the intervention will be underestimated, therefore collapsing the time points into larger segments (eg, quarters) or using advanced statistical methods is necessary; and (5) although the intervention group and control group do not need to be equivalent, the more comparable they are the more reliable the results [1, 2, 4].

Newland and colleagues use an interrupted time series design with a control group to determine the impact of a prospective-audit-with-feedback antimicrobial stewardship program (ASP) on antibiotic use [4]. They collected 50 months of antibiotic prescribing data preintervention and 34 months of antibiotic prescribing data post-ASP intervention at a single tertiary care children’s hospital. The control group consisted of 25 children’s hospitals that contributed complete antimicrobial utilization data to the Pediatric Health Information System over the same time period as the intervention hospital, but to the investigator’s knowledge did not implement an ASP. This research study lends itself well to this type of design as a prospective-audit-with-feedback intervention has an instantaneous impact on antibiotic utilization [5]. The study is further strengthened by collection of antibiotic prescribing data over 84 months and the use of AutoRegressive Integrated Moving Average modeling to analyze the data [2]. This type of analysis allows for proper identification and control of autocorrelations (eg, the dependency of two observations separated by a single time point) and secular trends. Limiting the control group to only the hospital members of Child Health Corporation of America that submitted complete antimicrobial prescribing data eliminates the potential for missing data. One remaining concern is the lack of additional information on the comparativeness of the whole control group to the hospital in which the ASP intervention occurred. For instance, if some of the control hospitals introduced a similar ASP intervention during the study period, the difference in effect between the pretest and posttest period may have been diluted and the true effect of the intervention would be greater than reported.

In summary, a quasi-experimental study is a useful way to answer questions within the field of infectious diseases when a randomized controlled trial is not appropriate. Using a quasi-experimental design with an interrupted time series and a control group, Newland and colleagues showed a strong temporal relationship between prospective-audit-with-feedback ASP and a decrease in days on antimicrobial therapy and length of antimicrobial therapy.

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